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REMARKS

No claims have been amended. Claims 1-9, 11, 12, 14, 17-20, and 25-28 are pending. Claims 1-4, 6-9, 11, 12, 14, and 17-20 have been rejected. Claims 5 and 25-28 have been objected to.

Oath/Declaration

On the Office Action Summary sheet, the Examiner indicated that the oath or declaration was objected to. However, the Office Action contains no explanation of the objection. Applicant believes that the Supplemental Declaration submitted on March 31, 2003, fully complies with the relevant statutes and rules. Applicant therefore requests clarification as to the nature of the objection.

Claim Rejections

Claims 1-4, 6-9, 11, 12, 14, and 17-20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Bordignon *et al.* (WO 95/06723, March 9, 1995) in view of Valenzuela *et al.* (WO 97/21811, June 19, 1997). The Examiner alleges that Bordignon *et al.* teach methods that comprise all the steps recited in the instant claims except the use of a cell surface mMuSK-R or MuSK-R as an identification marker for the genetically modified mammalian cells. The Examiner alleges that Valenzuela *et al.* teach various embodiments of rat and human muscle specific kinase receptors, including their extracellular, transmembrane, and intracellular domains, as well as an antibody that specifically binds the MuSK receptor. The Examiner further alleges that Valenzuela *et al.* teach that a MuSK-R is expressed in normal and denervated muscles, as well as other tissues including heart, spleen, ovary or retina.

The Examiner then alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce and use mMuSK-R in view of the teachings of Bordignon *et al.* and Valenzuela *et al.* for identifying the genetically modified hematopoietic cells or for the immunoselection of transduced mammalian cells with a reasonable expectation of success. The Examiner alleges that one would have been motivated to do so because (i) Bordignon *et al.* teach the use of a mutated cell surface receptor for identifying genetically modified

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mammalian cells including human hematopoietic cells or for immunoselection/immunoseparation of transduced mammalian cells; and (ii) Valenzuela *et al.* teach a cell surface MuSK-R and its extracellular domain, transmembrane domain, and intracellular domain, which can be used to make a mMuSK-R. The Examiner alleges that it would also have been obvious to one having ordinary skill in the art at the time the invention was made to use a MuSK-R as a masking marker with a reasonable expectation of success because expression of MuSK-R in human hematopoietic cells would not be expected to effect any signal transduction and to interfere with the functions of the cells since a MuSK-R is not expressed in human hematopoietic cells, and thus it is effective and useful in gene therapy.

Applicant respectfully traverses.

A. Legal Requirements for Obviousness

Both the burden of proof and the evidentiary standard for determining obviousness are precisely defined. Specifically, the Examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) the teaching or suggestion of all the claim limitations of the Applicant's invention in the combined prior art references; and, 3) a reasonable expectation of success. MPEP § 2143.

With regard to the first of these factors, suggestion or motivation to combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, it must be specific. The Federal Circuit recently re-emphasized in *In re Lee* the importance of specific motivation to combine references, stating:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g., McGinley v. Franklin Sports, Inc.*, 262

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F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).

"The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (*quoting C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("teachings of references can be combined only if there is some suggestion or incentive to do so.") (emphasis in original) (*quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In re Lee, 61 USPQ2d 1430, 1433-4 (Fed. Cir. 2002) (vacating and remanding the decision of the Board for failing to follow the relevant precedent).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. *See A-Site Corp. v. VSI International Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

B. The Examiner Has Failed to Provide an Expressed or Implied Motivation to Combine The Cited References

The Examiner is required to show how and why the Applicants would have been motivated to combine the references in the manner combined by the Examiner. The Examiner

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has not done so, but has simply made conclusory statements regarding the alleged motivation of a person of ordinary skill in the art to undertake the components of the claimed invention.

Although mentioning motivation, the Examiner has not shown it, but has simply summarized the teachings of the two cited references, stating:

one would have been motivated to [produce and use mMuSK-R in view of the teachings of Bordignon *et al.* and Valenzuela *et al.* for identifying the genetically modified hematopoietic cells or for the immunoselection of transduced mammalian cells] because (i) Bordignon *et al.* teach the use of a mutated cell surface receptor for identifying genetically modified mammalian cells including human hematopoietic cells or for immunoselection/immunoseparation of transduced mammalian cells. Such a mutated receptor with the intracellular domain either being partially or completely deleted cannot, after binding to its binding partner, effect any signal transduction, and thus is effective and useable in gene therapy; and (ii) Valenzuela *et al.* teach a cell surface MuSK-R and its extracellular domain, transmembrane domain, and intracellular domain, which can be used to make a mMuSK-R.

Merely summarizing the teachings of the two references does not constitute a showing of motivation to combine them. The Examiner alleges, in essence, that because various components of the invention were available at the time the present invention was made, it would have been *prima facie* obvious to one of ordinary skill in the art to combine them to obtain Applicant's claimed invention.

Though the motivation to combine prior art does not have to be expressly stated in the references themselves, "the examiner must present a convincing line of reasoning" for a proper conclusion that an invention is obvious in view of prior art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See also, *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In the instant case, the Office Action does not set forth any convincing reasoning as to the rationale behind combining the cited references. Indeed, when relying on a "scientific reasoning" rationale for combining references, the Examiner must provide evidentiary support for the existence and meaning of that scientific theory. See, *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979). Here, the Examiner has failed to meet this burden. The Examiner has neither identified an explicit suggestion in the prior art to combine the references nor has the Examiner provided the requisite evidence of a scientific rationale for combining the references.

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In view of the above, Applicant respectfully submits that the brief summary of what the prior art generally teaches falls far short of the requisite motivation to combine the cited references to produce Applicant's claimed method of using MuSK-R's as identification markers for genetically modified mammalian cells. The Examiner has provided no evidence at all to support the statement purporting to show motivation.

C. The Rejection Has Been Based On Impermissible Hindsight

Because the Examiner did not make clear any specific understanding or principle within the knowledge of a skilled artisan that would motivate or suggest to one with no knowledge of Applicant's claimed invention to make the combination, Applicant submits that the Examiner used impermissible hindsight reconstruction in reaching the conclusion of obviousness. The only possible motivation to combine the cited references is found in the disclosure itself, and this cannot be properly asserted against the Applicant. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

An Examiner cannot use hindsight reconstruction to pick and choose among individual teachings with the objective of rejecting claims as obvious. Here, the Examiner's use of hindsight is clearly evidenced by the fact that the references cited by the Examiner as teaching the use of MuSK-R's as identification markers for genetically modified mammalian cells are essentially the same references cited by the Applicant in the specification. Bordignon *et al.* is cited on page 1 of the specification as teaching that cell surface molecules have been used as selectable cell markers. The Valenzuela *et al.* PCT application (WO 97/21811, June 19, 1997) relied on by the Examiner is not itself cited in Applicant's specification; however, corresponding journal articles published by Valenzuela *et al.* disclosing MuSK-R's are cited on page 6. Applicant respectfully submits that this is clear evidence of hindsight reconstruction of Applicant's invention.

Applicant has integrated MuSK-R's found in the prior art into selectable marker assays to create new and nonobvious methods for identifying/immunoselection of genetically modified mammalian cells. However, the case law is clear: "It is improper, in determining whether a

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person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher.'" *In re Lee*, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002) (citing *W.L. Gore v. Garlock, Inc.* 220 USPQ 303, 312-13 (Fed. Cir. 1983).

D. The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn

For the reasons set forth above, Applicant submits that (1) the Examiner has failed to establish the requisite motivation for combining the cited references in the manner suggested, and (2) the only possible motivation to combine these references is found in the disclosure itself, which amounts to an improper use of hindsight. As a result, *prima facie* obviousness has not been established against any of the pending claims. The outstanding rejection under 35 U.S.C. §103(a) should therefore be withdrawn.

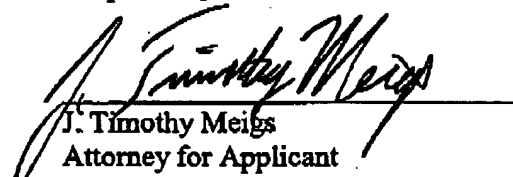
Conclusion

In view of the above amendments and remarks, it is submitted that this application is ready for allowance. Notice to this effect is solicited at the Examiner's earliest opportunity. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

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Respectfully submitted,


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